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Report

Calcium-Activated Myosin V Closes the *Drosophila* Pupil

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Summary

Approximately 40 years ago, an elegant automatic-gain control was revealed in compound eye photoreceptors: In bright light, an assembly of small pigment granules migrates to the cytoplasmic face of the photosensitive membrane organelle, the rhabdomere, where they attenuate waveguide propagation along the rhabdomere [1–3]. This migration results in a "longitudinal pupil" that reduces rhodopsin exposure by a factor of 0.8 log units [3, 4]. Light-induced elevation of cytosolic free Ca^{2+} triggers the migration of pigment granules [5–7], and pigment granules fail to migrate in a mutant deficient in photoactivated TRP calcium channels [8, 9]. However, the mechanism that moves photoreceptor pigment granules remains elusive. Are the granules actively pulled toward the rhabdomere upon light, or are they instead actively pulled into the cytoplasm in the absence of light? Here we show that Ca^{2+}-activated Myosin V (MyoV) pulls pigment granules to the rhabdomere. Thus, one of MyoV's several functions [10, 11] is also as a sensory-adaptation motor. In vitro, Ca^{2+} both activates and inhibits MyoV motility [12–16]; in vivo, its role is undetermined. This first demonstration of an in vivo role for Ca^{2+} in MyoV activity shows that in *Drosophila* photoreceptors, Ca^{2+} stimulates MyoV motility.

Results and Discussion

We assayed photoreceptor pigment-granule migration by observing an optical phenomenon called the deep pseudopupil (DPP) [17]. Upon illumination, the *Drosophila* DPP typically changes from dark red to bright green with a time constant as small as 2 s [3, 18]. In dark-adapted Canton-S wild-type eyes, the reflectance of the DPP is low; incident light is effectively channeled into the rhabdomeres and propagates there until it is absorbed by the visual pigment or by the pigment proximal to the rhabdomeres. Within seconds after the light is turned on, DPP reflectance rapidly increases, as pigment granules in the photoreceptor cytoplasm migrate to the rhabdomere base (Figure 1, Figure 5, left, and Movie S1 available online). The reflecting pigment granules cause a gold-green crescent in the light-adapted DPP. Note that although the pigment granules do not enter the rhabdomere, some of the light they reflect propagates distally along the rhabdomere, back to the source, seen as a dimmer central glow within the brighter crescent at the rhabdomere base (Figure 1) [18]. The pupil remains closed in the presence of continued strong light (Figure 1).

In a strong MyoV loss-of-function mutant, $MyoV^{KG04384}$, the pupil does not close, even after prolonged, bright illumination (Figure 1). Transgenic MyoV expression rescues $MyoV^{KG04384}$ pupil closure (Figure 1). In fact, even when adapted to the dark, the pupil of transgenic animals appears partially closed, probably reflecting MyoV overexpression (Figure 1).

We used electron microscopy to identify pigment granule position in dark- and light-adapted wild-type and MyoV mutant photoreceptors. To localize pigment granules in dark-adapted photoreceptors, we fixed eyes by using infrared illumination and image-intensifying eyepieces. Cytoplasm adjacent to the rhabdomere excludes most organelles and appears relatively clear in electron micrographs (Figure 2). This cytoplasmic domain is dominated by the rhabdomere terminal web (RTW), a dense array of parallel, polarized terminal web microfilaments that emanate brush-like from the rhabdomere base and extend deep into photoreceptor cytoplasm [19, 20]; RTW microfilaments are oriented with their plus ends, toward which MyoV motility is directed, to the rhabdomere base [19]. RTW cytoplasm is manifest as relatively clear cytoplasm from which organelles are excluded. As previously reported for *Musca* photoreceptors [2] and in *Drosophila trp* mutant photoreceptors [8], pigment granules of dark-adapted wild-type photoreceptors stand off from the rhabdomere base; they are separated from it by RTW cytoplasm and are located along the back, or minus side, of the RTW (Figure 2A). By 2 min after the room's lights come on, most pigment granules have moved through RTW cytoplasm to the rhabdomere base (Figure 2B). In dark-adapted $MyoV^{KG04384}$ photoreceptors, pigment granules still line up mostly along the back of the RTW (Figure 2C); few migrate in response to illumination (Figure 2D). MyoV is thus essential for pigment granule migration.

We used confocal immunofluorescence microscopy to ask whether MyoV localizes to pigment granules and migrates upon illumination. Because Lightoid (Ltd), a Rab-related protein, marks pigment granules [21], we double stained dark-adapted and illuminated photoreceptors with anti-MyoV and -Ltd antibodies. In dark-adapted photoreceptors, MyoV and Ltd localized prominently along a line at the back of RTW cytoplasm (Figure 3A), consistent with the electron microscopic localization of pigment granules. It is notable that this line persists in w^{1118} mutants that lack the ommochrome pigment granules [22], suggesting that pigment granules per se are not necessary for MyoV and Ltd localization. Ltd is also prominent in large vesicles, appearing as bright circles, in pigment cells that surround photoreceptors. Both MyoV and Ltd immunofluorescence in wild-type eyes are similar, but dimmer, presumably as a result of fluorescence quenching by the dense ommochrome pigment (data not shown). Upon illumination, MyoV and Ltd move to the rhabdomere base (Figure 3A). We thus conclude that pigment granules, Ltd, and MyoV migrate together upon Ca_i increase.

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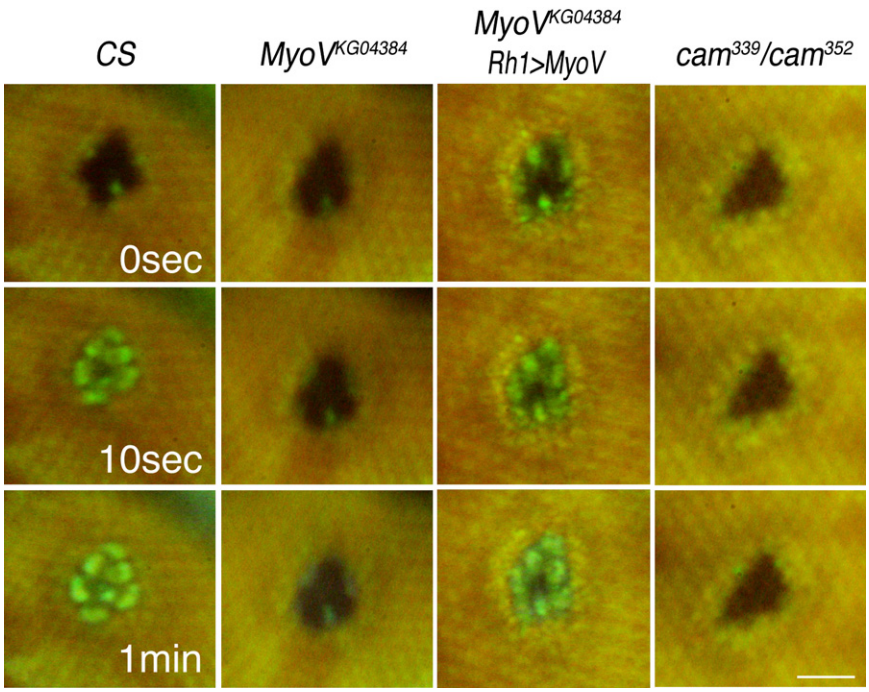

Figure 1. The Pupil Fails in MyoV and CaM Mutants

Natural reflectance of the DPP under incident white light at 0 s, 10 s, and 1 min after lights on. Canton-S DPPs reflect bright green-gold before 10 s strong illumination. In *MyoV*^{KG04384} and *cam*^{339}/*cam*^{352} hetroallelic hypomorphs, DPPs do not reflect, even after 1 min illumination. Transgenic restoration of MyoV rescues the pupil; some reflectance is seen even in dark-adapted retinas. Note that the DPP comprises the magnified, superposed virtual images of approximately 20 ommatidia and is readily visible at low magnification; all subsequent images are of individual ommatidia. The scale bar represents 50 μm.

In Ltd-null, *ltd*^{1} mutants, MyoV's characteristic localization is lost: MyoV is diffuse throughout the cytoplasm of both dark-adapted and illuminated photoreceptors (Figure 3B). The formation of pigment granules in *ltd*^{1} mutants is impaired, and there are few ommochrome granules in *ltd*^{1} photoreceptors [23] (also data not shown). However, decreased pigment granule number cannot account for MyoV delocalization because MyoV localizes normally in *w*^{1118} photoreceptors, which contain Ltd but not pigment granules. Thus, Ltd is essential for MyoV's localization in dark-adapted photoreceptors and its light-dependent translocation to the rhabdomere base.

To evaluate potential interactions between Ltd and MyoV, we used binary yeast two-hybrid assays (Figure 3C). We found a strong interaction between Ltd's Rab domain and the MyoV tail (amino acids 922–1800). A medium length of MyoV tail (amino acids 1063–1800) showed weak interaction, but the shortest tail fragment (amino acids 1383–1800) did not support colony growth. Direct protein-protein interaction is supported by coimmunoprecipitation of Ltd's Rab domain and a long fragment of MyoV tail from an in vitro transcription and translation system (Figure 3D).

Vertebrate MyoV binds CaM [12], and *Drosophila* MyoV binds CaM and Myosin light chain-cytoplasmic (Mlc-c) when the proteins are coexpressed in cells [24]. Consequently, we investigated CaM and Mlc-c localization in dark-adapted and illuminated photoreceptors (Figure 4A; Figures S1 and S2). CaM localized along the back of the RTW cytoplasm in dark-adapted photoreceptors. Lighter, diffuse anti-CaM staining, not overlapping with MyoV, was also seen in rhabdomeres and cytoplasm (Figure 4A). Upon illumination, CaM and MyoV cotranslocate to the rhabdomere base (Figure 4A). Mlc-c translocates similarly (Figure S1). Both CaM and Mlc-c coimmunoprecipitate with Myc-tagged MyoV C-terminal (Figure 4D). Thus, both CaM and Mlc-c are photoreceptor MyoV light chains.

We next investigated the impact of CaM loss on MyoV localization. Although CaM-null flies are embryonic lethal, heteroallelic *cam*^{339}/*cam*^{352} flies expressing less than 10% wild-type CaM are viable [25]. CaM staining is greatly reduced in these animals, and MyoV localization is abnormal (Figure 4B). In both light and dark conditions, some MyoV localizes to rhabdomere tips, whereas it is otherwise diffuse in the cytoplasm. CaM is thus essential for normal MyoV distribution. Together, these results suggest that CaM binds MyoV and, in response to illumination, they move together across the RTW.

We assayed DPP reflectance in *cam*^{339}/*cam*^{352} flies. Similar to what is seen in MyoV mutants, the pupil does not close in these flies, even after bright, continuous illumination (Figure 1). In electron micrographs of dark-adapted *cam* mutants, pigment granules are positioned normally (data not shown). In illuminated *cam*^{339}/*cam*^{352} photoreceptors, pigment granules still line up along the back of the RTW; pigment granule translocation is completely abolished (Figure 4C). CaM is thus essential for the migration of pigment granules.

It is important to efficiently integrate MyoV motility with the specific cellular task at hand. Upon illumination, *Drosophila* phototransduction entrains rises of Ca_i, from 160 nM in the dark to 10 μM in bright light [26]; pigment-granule migration is triggered at 1 μM Ca^{2+}, a level attained at luminances above 0.3 cd/m^2 [5–7], which is roughly comparable to the threshold of human color vision [18]. As in the pupil, Ca^{2+} elevation stimulates purified chick brain MyoV ATPase activity 90-fold over baseline activity [12], and there is a sharp activation threshold at 1 μM Ca^{2+} [12]. In vitro, low Ca^{2+} unfolds and activates MyoV, whereas higher Ca^{2+} dissociates CaM from MyoV lever arms and inhibits motility; addition of exogenous CaM restores motility [15, 16, 27]. Results here suggest that the endogenous pool of CaM in fly photoreceptors suffices to preserve motility in the presence of elevated Ca^{2+}.

Cargo binding to the MyoV globular tail in vitro also promotes MyoV unfolding and activation [15, 28–31], raising the question of whether vesicle-bound MyoV in vivo must be constitutively active. Results here suggest this may not be necessary; in the dark, pigment granules localize to the back of the RTW, indicating cargo-bound MyoV activation additionally requires Ca^{2+} signaling. Ltd linkage of pigment granules might allow an extended MyoV form that is inactive at resting Ca_i.

MyoV frequently partners with Rab family proteins to mediate organelle transport [32]. In *Drosophila* photoreceptors,

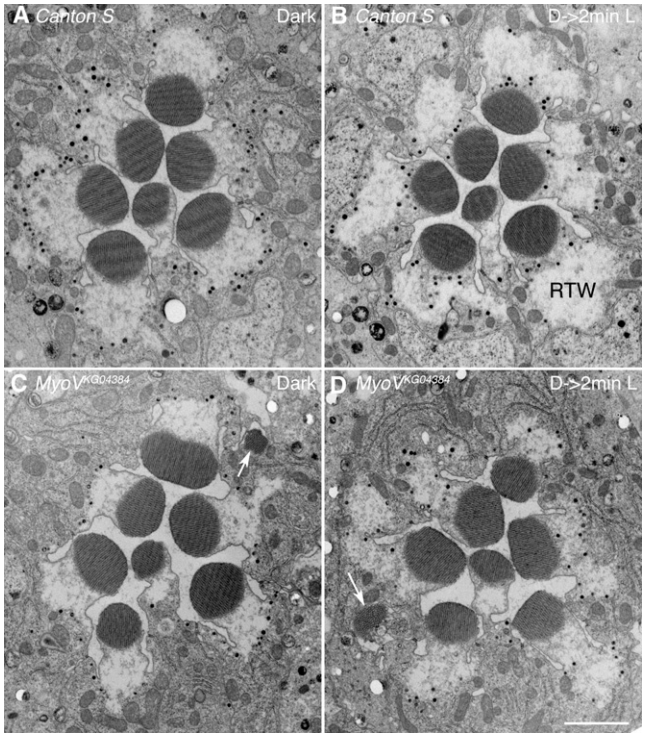

Figure 2. Pigment Granules Fail to Migrate in MyoV Mutant Photoreceptors

(A) An electron micrograph of a dark-adapted, newly eclosed Canton-S ommatidium, dissected and fixed with infrared eyepieces (dark fixation), shows ommochrome pigment granules positioned behind organelle-poor RTW cytoplasm.

(B) By 2 min after the room's light (ca. 800 lux) came on, most pigment granules have migrated to the rhabdomere base; some remain behind.

(C) In dark-adapted newly eclosed *MyoV*^{KG04384}, pigment granules are positioned normally behind RTW cytoplasm.

(D) By 2 min after the room's lights came on, some *MyoV*^{KG04384} pigment granules have moved to the rhabdomere base, but most remain behind. Arrows in (C) and (D) point to ectopic rhabdomeres, often seen in *MyoV*^{KG04384} photoreceptors [33]. The scale bar represents 2 μm.

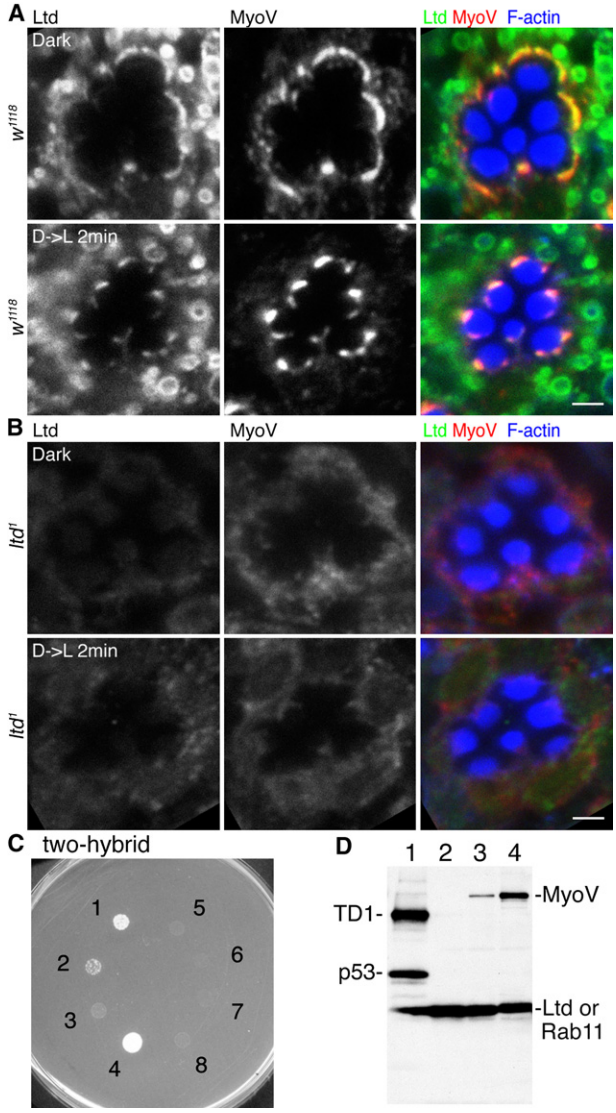

Figure 3. Ltd Couples MyoV to Pigment Granules

(A) Newly eclosed w^{1118} flies stained for Ltd (green), MyoV (red), and F-actin (blue). In dark-adapted w^{1118} photoreceptors, MyoV and Ltd colocalize prominently along a line behind RTW cytoplasm; staining is absent at the rhabdomere base. By 2 min of light exposure, MyoV and Ltd have localized to the rhabdomere base, particularly along the "edges" of the base. Ltd staining outlines large vesicles in the pigment cells, consistent with previous immuno-electron microscope localization [21].

(B) Newly eclosed ltd^1 flies stained for Ltd (green), MyoV (red), and F-actin (blue). In ltd^1 flies, MyoV is diffuse in the cytoplasm of both dark-adapted and illuminated photoreceptors.

(C) Colony growth assay. (1) MyoV 922-1800 +Ltd, (2) MyoV 1063-1800 +Ltd, (3) MyoV 1383-1800 + Ltd, (4) p53 +TD1 (positive control), (5) MyoV 922-1800 +p53 (negative control), (6) MyoV 1063-1800 +p53 (negative control), (7) MyoV 1383-1800 +p53 (negative control), and (8) Ltd +TD1 (negative control). The longest MyoV tail (amino acids 992–1800) strongly interacted with Ltd Rab domain. The medium-length MyoV tail (amino acids 1063–1800) showed weak interaction, but the shortest tail fragment (amino acids 1383–1800) did not support colony growth.

(D) Ltd Rab domain-MyoV coimmunoprecipitation. Mixed transcription and translation products are indicated at right. We used anti-Myc antibody for immunoprecipitation. Bound protein retained on beads after the final wash is shown. Myc Ltd does not coimmunoprecipitate HA-TD1. Both Myc-Ltd and Myc-Rab11 coimmunoprecipitate HA-MyoV. The scale bar represents 2 μm.

distinct Rab family members harness MyoV to distinct activities. In differentiating photoreceptors Rab11 partners with MyoV to deliver post-Golgi biosynthetic traffic to the rapidly expanding sensory membrane [33]. In mature photoreceptors, Ltd couples MyoV to pigment granules, employing it as a motor of sensory adaptation (Figure 5).

MyoV positions melanosomes within melanocytes, delivers recycling and biosynthetic vesicles to the plasma membrane, propels endosomal traffic in neurons, and carries vacuoles into budding yeast daughter cells [10, 34]. Loss of MyoV-dependent motility causes human Griscelli disease, whose patients suffer hypopigmentation and neurological and immunological defects (OMIM 214450) [35]. Mutant mice lacking MyoV are hypopigmented and fail to deliver Ca^{2+}-regulating endosomes to synaptic spines; they suffer severe, often fatal seizures [36, 37]. The *Drosophila* pupil is a genetically and molecularly tractable in vivo assay for this vital cellular motor.

Supplemental Data

Experimental Procedures, two figures, and a movie are available at http://www.current-biology.com/cgi/content/full/18/13/951/DC1/.

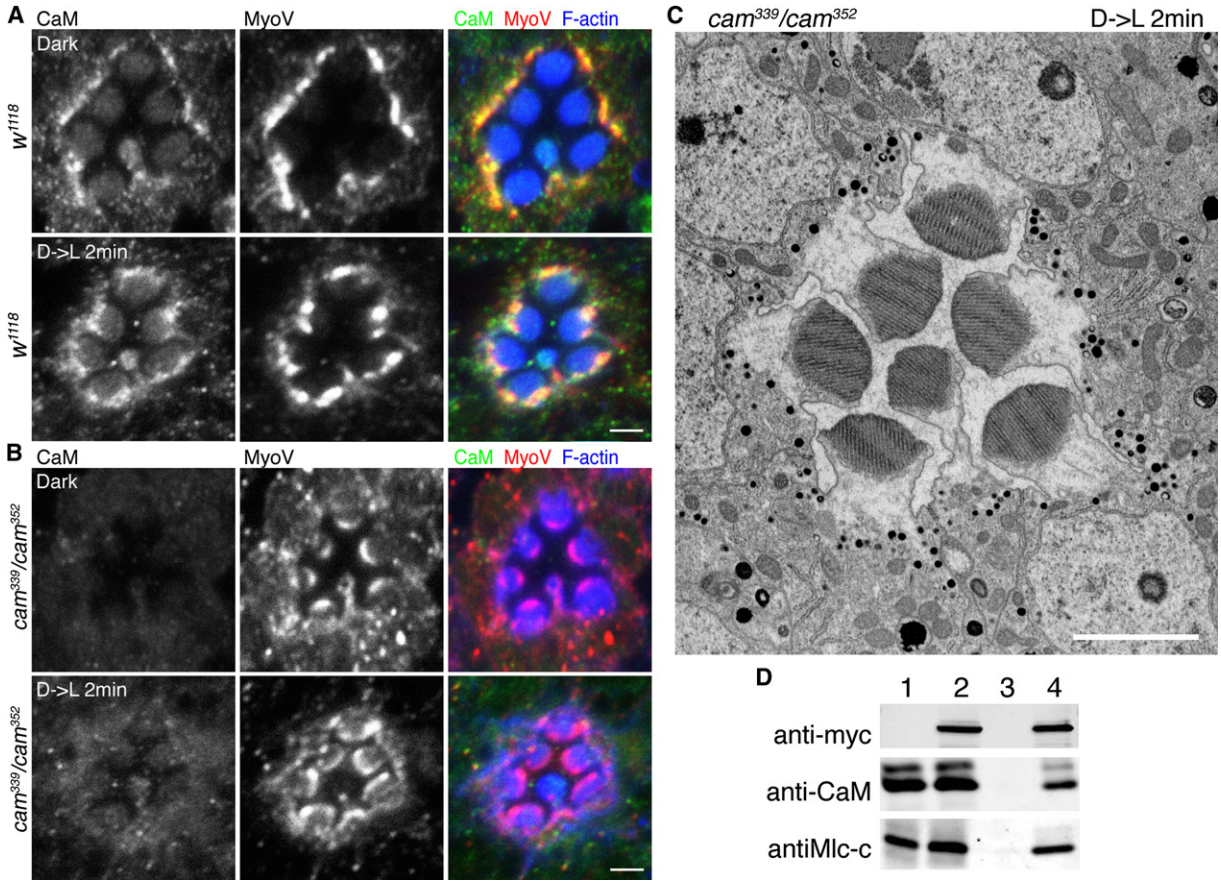

Figure 4. CaM Colocalizes with MyoV and Is Essential for Normal MyoV Localization

(A) Newly eclosed w^{1118} flies stained for CaM (anti-*Dictyostelium* CaM: green), MyoV (red), and F-actin (blue). CaM is detected in rhabdomeres and cytoplasm, where it colocalizes prominently with MyoV. In the dark, CaM localizes prominently along the back of RTW cytoplasm and, after 2 min of light, CaM localizes to the rhabdomere base.

(B) Dark-adapted and 2-min-illuminated cam^{339}/cam^{352} heteroallelic ommatidia are stained for CaM (anti-*Dictyostelium* CaM: green), MyoV (red), and F-actin (blue). In cam^{339}/cam^{352} heteroallelic hypomorphs, CaM staining is weak, and MyoV delocalized. In both dark and illuminated conditions, MyoV localizes at rhabdomere tips and is diffuse in the cytoplasm. A second anti-CaM antibody (from K. Beckingham) showed a similar staining pattern, but another anti-CaM antibody (from C. Klee) visualized mainly rhabdomeric CaM (Figure S2).

(C) An electron micrograph of a 2-min-illuminated cam^{339}/cam^{352} heteroallelic hypomorph ommatidium shows ommochrome pigment granules positioned behind organelle-poor RTW cytoplasm. The scale bar represents 2 μm.

(D) Coimmunoprecipitation of CaM and Mlc-c by Myc-MyoV-CT. Lanes 1 and 2, extracts from w^{1118} and Rh1gal4 > Myc-tagged MyoVCT heads, respectively. Lanes 3 and 4, anti-Myc immunoprecipitants from w^{1118} and Rh1gal4 > Myc-tagged MyoVCT heads, respectively. Neither CaM nor Mlc-c is coimmunoprecipitated from control w^{1118} heads (lane 3). Myc-tagged MyoVCT immunoprecipitates both CaM and Mlc-c from Rh1Gal4 > Myc-MyoVCT heads (lane 4).

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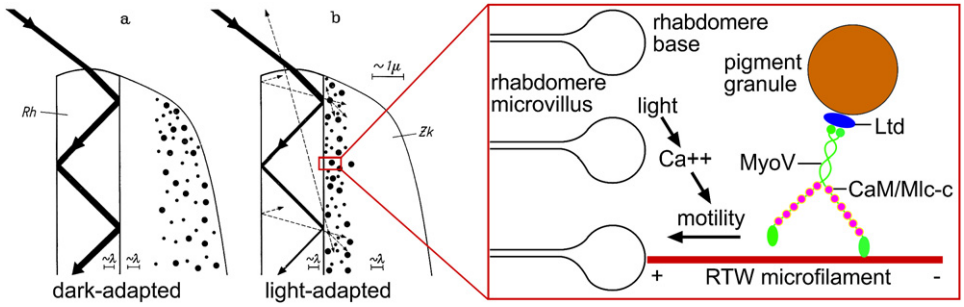

Figure 5. The Longitudinal Pupil

(Left) Drawing from Kirschfeld and Franceschini, 1969 [1], showing light (bold, arrowed) channeling efficiently along dark-adapted rhabdomeres (Rh). Pigment granules of dark-adapted photoreceptors localize away from the base and promote waveguide propagation. In light-adapted photoreceptors, pigment granules at the rhabdomere base degrade waveguide propagation and rhodopsin exposure; light backscattered by pigment granules (dashed lines) increases DPP reflectance. (Right) A model mechanism for the longitudinal pupil (not to scale). Ltd links MyoV to pigment granules. Both CaM and Mlc-c bind the long, multi-IQ domain MyoV lever arms. Upon illumination, $Ca2^{+}$ elevation promotes MyoV motility and pulls pigment granules to the plus ends (+) of RTW microfilaments at the base of the rhabdomere.

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